Surface adsorption of lattice HP proteins: Thermodynamics and structural transitions using Wang-Landau sampling

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Abstract

Wang-Landau sampling has been applied to investigate the thermodynamics and structural properties of a lattice hydrophobic-polar heteropolymer (the HP protein model) interacting with an attractive substrate. For simplicity, we consider a short HP sequence consisting of only 36 monomers interacting with a substrate which attracts all monomers in the sequence. The conformational "phase transitions" have been identified by a canonical analysis of the specific heat and suitable structural observables. Three major "transitions", namely, adsorption, hydrophobic core formation and "flattening" of adsorbed structures, are observed. Depending on the surface attractive strength relative to the intra-protein attraction among the H monomers, these processes take place in different sequences upon cooling.

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I. INTRODUCTION

Protein folding and protein adsorption have long been subjects of intense research. The topics gained so much attention both because of their numerous applications in nanotechnology, biomaterials, medical and biological sciences (see e.g., [1–3] and references therein), but also because of the many interesting, yet challenging, basic scientific questions they pose. However, due to the complexity of the problems, our understanding of protein structure and folding is still incomplete and a "general theory" is lacking. The difficulties arise from the many interactions, of various strengths, among the building blocks constituting the protein organizing the molecules into primary, secondary or tertiary structures [4].

Additional protein-substrate interactions add a further level of complexity to the problem. When brought in the vicinity of a substrate, a protein rearranges its configuration to differ from its native state. Generally, the nature of surface adsorption depends on the properties of the protein, surface and interactions, but many details remain unsolved [3, 5, 6].

Simplified protein models that capture the essential features of real proteins have thus been proposed in hope of unraveling the mysteries. Such coarse-grained models have the advantage of being readily accessible to computer simulation. With the emerging computer power nowadays, numerical simulation of such protein models play therefore an ever important role to the understanding of the problems. Nevertheless, they are still computationally intensive and unexpectedly difficult despite the simplicity of the models. In this work, we will investigate the hydrophobic-polar (HP) lattice protein model [7] (one of the simplest such model), subjected to an attractive surface. Thereby, we attempt to understand the thermodynamic and *generic* structural behavior of protein adsorption from a statistical mechanics point of view. Furthermore, we will study the influence of the strength of substrate attraction on the adsorption and folding processes of an HP protein.

II. MODEL

In an aqueous environment, a protein's hydrophobic amino acids tend to stay away from the solvent and form an interior core, while polar amino acids form an exterior shielding shell [8, 9]. This is known as the hydrophobic effect and is believed to be the driving force for the formation of tertiary structures [10–12]. The HP model [7] is a prototypical, coarse-grained

lattice protein model introduced to mimic this phenomenon. It classifies amino acids into two types of monomers according to their affinity to water: hydrophobic (H) and polar (P). Interactions are restricted to an attractive coupling, of strength ε_{HH}, between non-bonded hydrophobic monomers occupying nearest-neighbor sites.

To simulate protein adsorption, an attractive substrate is placed at $z = 0$ on a 3-dimensional cubic lattice [13]. For simplicity, in this work we consider a surface that attracts all monomers with a strength ε_S. The energy of the system is then given by:

$$E = -\varepsilon_{HH} n_{HH} - \varepsilon_S n_S, \tag{1}$$

n_{HH} being the number of H-H interacting pairs and n_S being the number of monomers adjacent to the bottom surface. In addition, a non-attractive wall is placed at $z = N + 1$ to confine the HP chain from above, where N is the number of monomers in the sequence. The purpose of placing the steric upper wall is to limit the vertical translational degrees of freedom of the protein, so as to shorten the time spent on simulating desorbed conformations. Figure 1 shows a schematic diagram of the model. Here, we have used a 36mer $(P_3H_2P_2H_2P_5H_7P_2H_2P_4H_2P_2HP_2)$ [14] to illustrate the effect of ε_S on the structural "phase transitions" associated with protein adsorption.
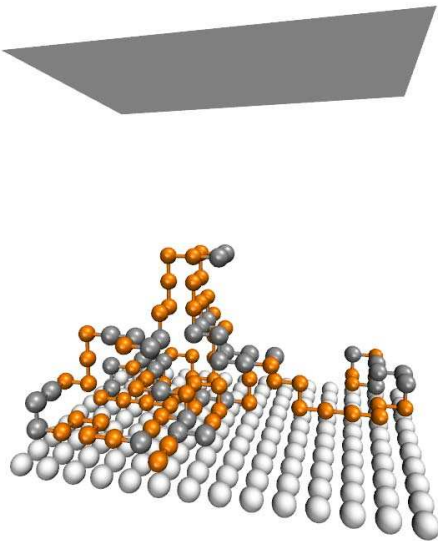

FIG. 1. A schematic diagram showing the model used in this work. The gray spheres represent hydrophobic monomers, orange spheres represent polar monomers, faint spheres are the attractive molecules of the substrate and the solid top surface is non-attractive.

III. METHODS

A. Wang-Landau sampling and production run

In order to investigate such conformational transitions, it is necessary to have a mean of sampling a protein's entire conformational/energy space efficiently. Here, in the first stage of the simulation, Wang-Landau (WL) sampling [15–18] has been employed to estimate the energy density of states, $g(E)$, which then gives access to thermodynamic quantities at any temperature. In this iterative procedure, a trial configuration of energy E_{trial} is generated with an acceptance probability inversely proportional to $g(E_{trial})$. The old configuration is retained if the trial one is rejected. A multiplicative modification factor f (with an initial value $f_{init} = e^1$ at the beginning of the simulation) is used to modify $g(E)$, i.e., $g(E) \rightarrow g(E) \times f$. A histogram in energy is also accumulated: $H(E) \rightarrow H(E) + 1$. When a "flat" histogram is attained, the simulation is brought to the next iteration: $H(E)$ is reset and f is reduced, $f \rightarrow \sqrt{f}$. A "flat" histogram is defined as when all entries in $H(E)$ are greater than $p \times H_{ave}$, where p is the flatness criterion and H_{ave} is the average of all entries in $H(E)$. All results presented in this work are obtained by using a flatness criterion $p = 0.8$ for reliable estimates of $g(E)$. The simulation is terminated when $\ln(f_{final})$ reaches a preset minimum value of 10^{-8}.

The partition function, $Z(T)$ and subsequent thermodynamics, e.g. average energy $\langle E \rangle_T$ and specific heat $C_V(T)$, then follow:

$$Z(T) = \sum_i g(E_i)e^{-E_i/kT}, \tag{2}$$

$$\langle E \rangle_T = \frac{1}{Z(T)} \sum_i E_i g(E_i)e^{-E_i/kT}, \tag{3}$$

$$C_V(T) = \frac{1}{kT^2} \left(\langle E^2 \rangle - \langle E \rangle^2 \right), \tag{4}$$

where k is the Boltzmann constant, T is the temperature and the sum runs over all possible energies.

The second stage of the simulation consists in a production run making use of multi-canonical sampling [19, 20] to generate a number of two-dimensional densities of states, $g(E, Q)$, where Q is any structural quantity of interest, such as e.g., the radius of gyration

$R_g = \sqrt{\frac{1}{N} \sum_i^N (\vec{r}_i - \vec{r}_{cm})^2}$ ($\vec{r}_i$ is the position of the ith monomer and $\vec{r}_{cm}$ is the position of the center of mass), the number of surface contacts n_S, the number of surface contacts of hydrophobic monomer n_{SH}, the number of surface contacts of polar monomer n_{SP}, or the number of hydrophobic interaction pairs n_{HH}. During the production run, the inverse of $g(E)$, obtained from Wang-Landau sampling, is used as the weight of the acceptance rate, while structural quantities are calculated and two-dimensional histograms, $H(E,Q)$, are accumulated. At the end of the simulation, the $H(E,Q)$'s are reweighted by $g(E)$ in order to yield the two-dimensional densities of states, $g(E,Q)$'s. The partition function of an observable Q, $Z_Q(T)$, and its expectation value can then be calculated as

$$Z_Q(T) = \sum_{E,Q} g(E,Q)e^{-E/kT}, \tag{5}$$

$$\langle Q \rangle_T = \frac{1}{Z_Q(T)} \sum_{E,Q} Q g(E,Q)e^{-E/kT}. \tag{6}$$

Thermodynamics of the structural quantities in addition to the specific heat, C_V, are essential in identifying "transitions" between different structural "phases". In cases where the specific heat shows ambiguous signals, structural quantities help clarifying the types of transition taking place at different temperatures. In some cases distinct signals might be missing in the specific heat, whereas structural quantities are more reliable to identify structural transitions.

B. Methodological pitfalls

Traditional Monte Carlo trial moves for lattice polymers either change a conformation locally (e.g. kink flip and crankshaft) or non-locally (e.g. pivot moves). Local moves generate new configurations fairly similar to the old ones as most parts of the polymer remains unchanged, inducing long correlation times in the simulation. Non-local moves do not share the same problem, but they are ineffective for dense conformations. Two inventive Monte Carlo trial moves, namely, pull moves [21] and bond-rebridging moves [22], have thus been implemented in our simulations to confront these problems. When combined with Wang-Landau sampling, they have proven to be particularly efficient in exploring conformational space [23, 24].

However, these non-traditional trial moves alone are not able to give correct low temperature thermodynamics if they are used with Metropolis sampling, which is easily trapped in metastable states. Figure 2 compares the two sampling methods, where the two transition peaks at low temperature in the specific heat are clearly missing in the Metropolis case. We thus stress that an appropriate combination of the sampling method and trial updates is crucial in obtaining correct results from a Monte Carlo simulation.
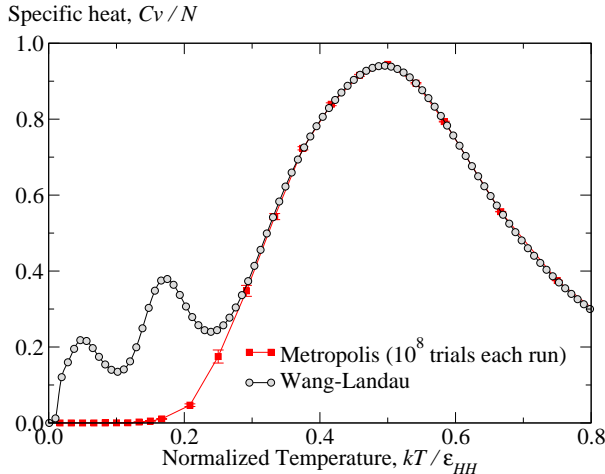

FIG. 2. Comparison between Wang-Landau and Metropolis sampling in obtaining the specific heat of a 36mer interacting with a very weak attractive surface, in which $\varepsilon_{HH} = 12\varepsilon_S$. Error bars smaller than the data points are not shown.

IV. RESULTS

A. Identifying structural "phase transitions"

The different structural "phase transitions" are best illustrated by considering the 36mer interacting with a very weak attractive surface ($\varepsilon_{HH} = 12\varepsilon_S$). Detailed studies of this system can be found in Refs.[25, 26]. As shown in Figure 3, its specific heat has three distinct peaks, which represent three basic phase transitions, respectively (from high to low temperature): (i) hydrophobic core (H-core) formation, (ii) adsorption, and (iii) "flattening" of the adsorbed structure.

These three transitions can be identified by comparing the peak positions of the specific heat and those of the structural quantities. The thermal derivative of $\langle n_{HH} \rangle$ peaks for H-core formation, while the thermal derivatives of $\langle n_{SH} \rangle$ and $\langle n_{SP} \rangle$ peak for adsorption at a higher temperature, and flattening at a lower temperature due to the fact that the flattening process has to take place after the protein is adsorbed on cooling. In some cases, it is also

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possible that flattening is signaled by a shoulder, or only a peak in either $\frac{d\langle n_{SH}\rangle}{dT}$ or $\frac{d\langle n_{SP}\rangle}{dT}$ but not both.
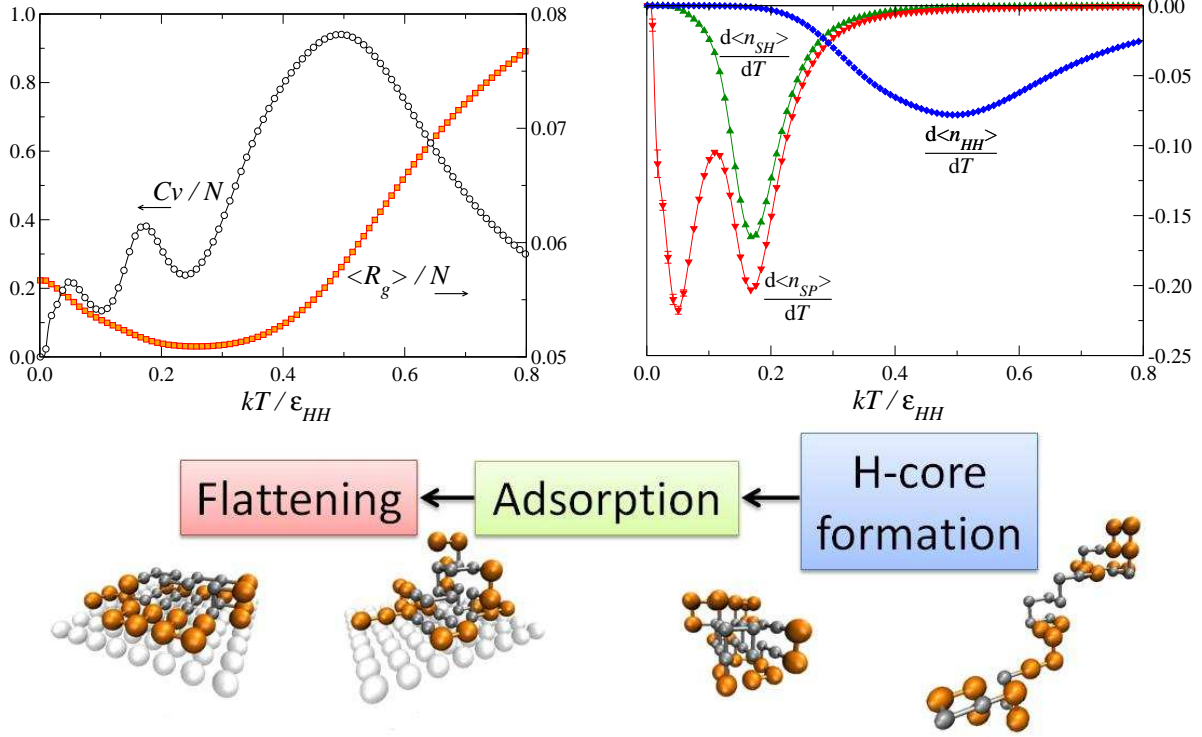

FIG. 3. Specific heat and structural quantities of the 36mer interacting with a very weak attractive surface ($\varepsilon_{HH} = 12\varepsilon_S$). Error bars smaller than the data points are not shown.

B. Effect of surface attraction on the sequence of transitions

The three basic transitions occur at different temperatures when the surface attractive strength varies, giving rise to a *different order* in structural changes. As a consequence, an extended, desorbed protein goes through a different path in conformational space towards the acquisition of compact, adsorbed ground states. Structures of the intermediate and ground states thus vary from case to case and are completely dependent on this sequence (or order) of transitions.

When the surface attraction becomes stronger, it first affects the transitions at higher temperatures. Figure 4 shows the thermodynamics for the 36mer interacting with a surface of moderate attractive strength ($\varepsilon_{HH} = 2\varepsilon_S$). Despite the fact that only two peaks are present

in the specific heat, the three basic transitions and their order of occurrence are revealed by the analysis of the structural parameters. Adsorption takes place at $kT/\varepsilon_{HH} \approx 1.0$ corresponding to the C_V peak at the higher temperature; a hydrophobic core forms at a slightly higher temperature ($kT/\varepsilon_{HH} \approx 0.35$) than that of flattening ($kT/\varepsilon_{HH} \approx 0.27$), and both processes are responsible for the C_V peak at the lower temperature.
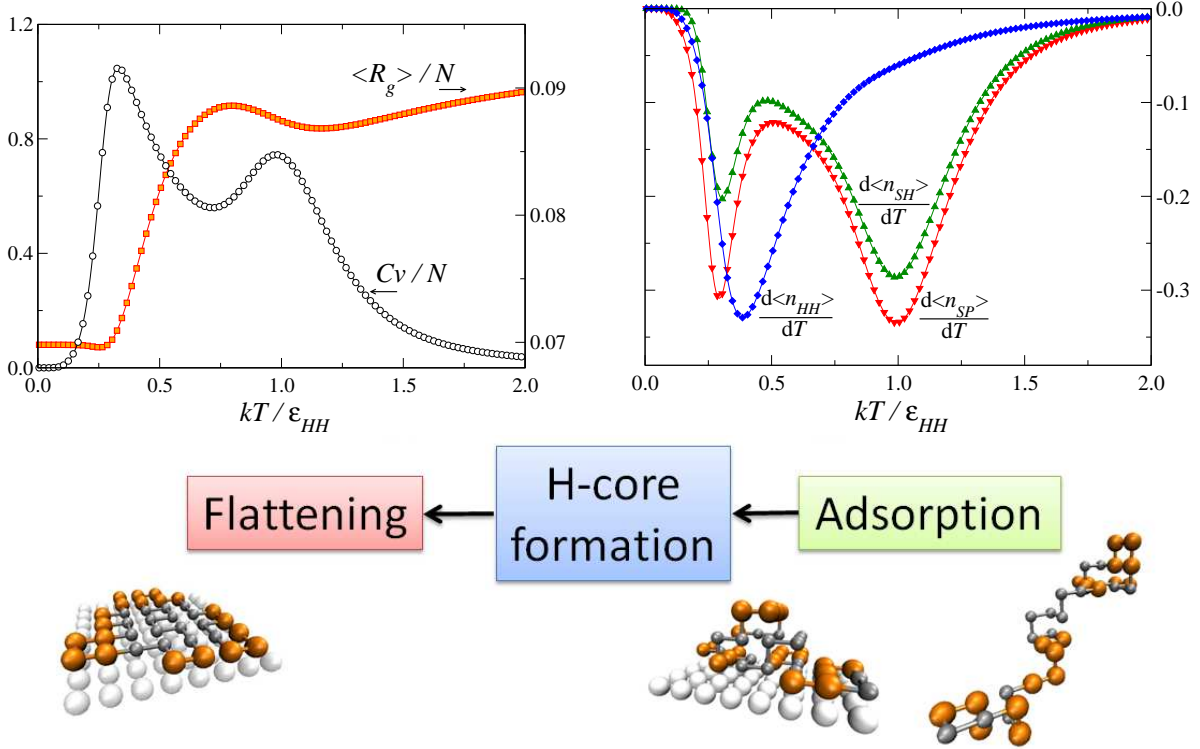

FIG. 4. Specific heat and structural quantities of the 36mer interacting with a moderately attractive surface ($\varepsilon_{HH} = 2\varepsilon_S$). Error bars are smaller than the data points.

In terms of the transition sequence, H-core formation and adsorption have swapped places compared to the former case. On cooling, a three-dimensional, adsorbed but extended structure is first formed after adsorption which takes place at the highest temperature. The lowest energy state with a two-dimensional hydrophobic core is achieved after the combined action of H-core formation and flattening. As these two processes closely overlap, no intermediate states could be singled out between them.

Further increase in surface attractive strength shifts the H-core formation to an even lower temperature as shown in Figure 5, where a strong attractive surface is used ($\varepsilon_{HH} = \frac{1}{2}\varepsilon_S$). In this case, there are also two peaks in the specific heat with a weak bump in between. A

comparison with the structural properties clearly distinguishes the three basic transitions, which now occur at well separated temperatures. Adsorption takes place at $kT/\varepsilon_{HH} \approx 4.0$; H-core formation at $kT/\varepsilon_{HH} \approx 0.4$; the bump occurs between $kT/\varepsilon_{HH} \approx 1.0$ and $kT/\varepsilon_{HH} \approx 3.0$ is a signal of flattening.

With this transition ordering, the desorbed, extended protein first adsorbs on the surface to form a three-dimensional, adsorbed yet extended structure. After the flattening process, most of the monomers contact with the surface but the chain is still not compact. The H-core formation finally takes place on the surface, forming a two-dimensional ground state with a hydrophobic core.
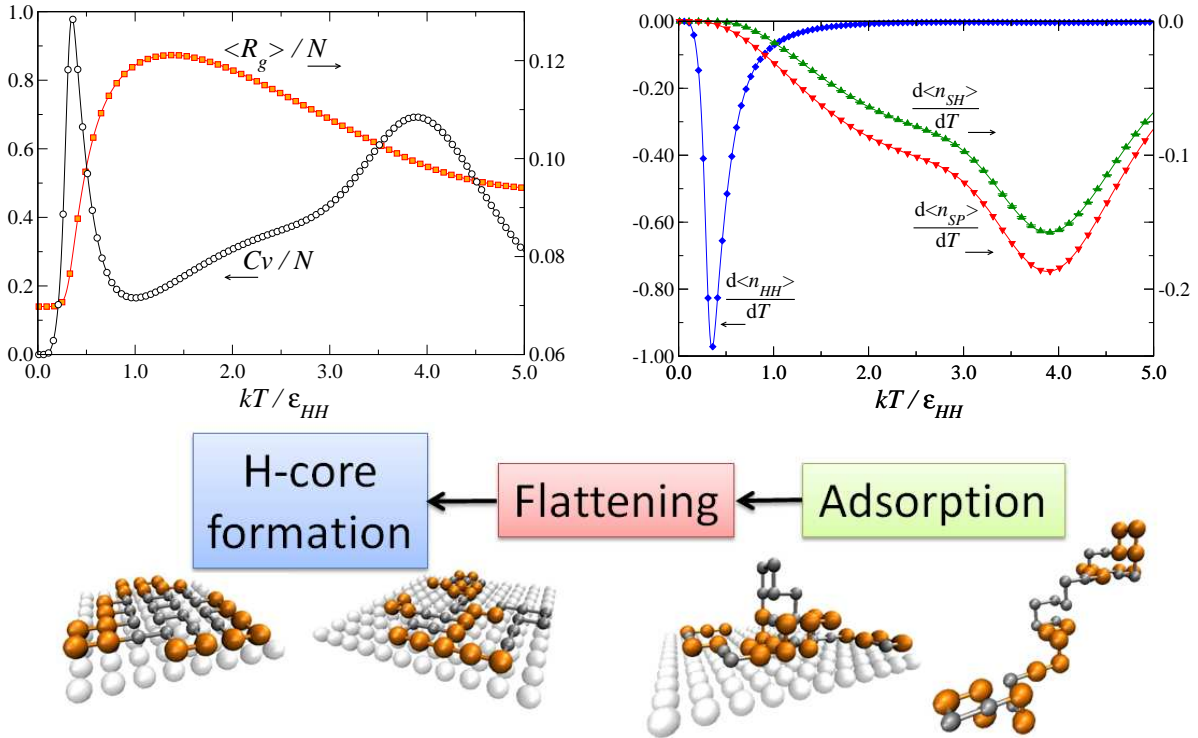

FIG. 5. Specific heat and structural quantities of the 36mer interacting with a strong attractive surface, in which $\varepsilon_{HH} = \frac{1}{2}\varepsilon_S$. Error bars are smaller than the data points.

V.   CONCLUSION

Protein adsorption has been studied using the HP lattice model and Wang-Landau sampling with efficient Monte Carlo trial updates. The combined thermodynamic signals of the specific heat and some suitable structural quantities allowed us to identify conformational

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"phase transitions". Three basic transitions, namely, hydrophobic core formation, adsorption and "flattening" of adsorbed structures, have been found to occur in a different sequence with varying surface attraction strength, ε_S, upon cooling. The acquisition of the adsorbed, compact, lowest energy states from a desorbed, extended coil thus goes through different paths in conformational space with different intermediates. The structures of ground state configurations may also differ from each other for different surface attractions.

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